REMARKS

Status of the Claims

Claims 3-14 and 21-25 are pending; claims 1-2, 22-23 and 26 are canceled; and all of the remaining pending claims are currently amended.

Claims 3-6 have been amended to recite that the concentration of cyclosporin in the administered composition is from 0.1% to 20% by weight and that the DMSO is present at least 80% by weight. Support for this amendment is found, for instance, in canceled claim 1.

Claims 4-6 have been amended to improve grammar.

Claim 7 has been amended so that it depends from claims 3, 4, 5 or 6.

Claims 11-12 and 24-25 have been amended so that they depend from claims 3, 4, 5 or 6 instead of canceled claim 1.

Claim 24 has been amended to recite that the dose of cyclosporin administered is 0.0001 to 200 mg/kg/day. Support for this amendment is found, for instance, in the last block of text on page 6 of the specification.

Claim 25 has been amended to recite a dose of cyclosporin of from 5 mg per day to 5000 mg (5 g) per day. Support for this amendment is provided at the last paragraph of page 6 of the specification

No new matter has been added.

1. Claim Rejections under 35 USC §103

The Examiner has rejected claims of 1-14 and 21-26 as allegedly obvious over Kaswan taken with Elzinga et al. (1989), Broadwell et al. (1982), Elias and Okonkwo et al. (Office Action, pages 3-8). Applicants respectfully traverse.

First of all, Applicants point out that composition claims 1 and 2 have been canceled. In addition, the limitations recited in canceled claim 1 reciting that the concentration of cyclosporin is from 0.1% to 20% by weight and that DMSO is present at 80% by weight in the composition have been imported into the presently pending method claims.

Next, Applicants point out that the Okonkwo publication is not prior art against this application because it was published in April of 1999, whereas the priority date for this application is the International Application (PCT) filing date of February 26, 1999. Accordingly, it is impermissible to rely on the teachings of Okonkwo et al. in the obviousness analysis.

So the present obviousness analysis is limited to Kaswan taken with Elzinga et al., Broadwell et al. and Elias. Here, Applicants point out that, of these four references, only Broadwell et al. teaches the administration of cyclosporin – DMSO. However, Broadwell et al. make NO mention of a cyclosporin-DMSO formulation and further they fail to disclose administration intraperitoneally and intravenously. None of the cited references teach the administration of DMSO itself, alone or with other agents and especially a composition of cyclosporin and DMSO, intracerebroventricularly or intrathecally into the CSF, or by inhalation.

In particular, Kaswan teaches the administration of cyclosporin in DMSO compositions **topically** to the eye. Elzinga et al. compares the effect of DMSO on cyclosporin absorption with that of conventional olive oil vehicles following **oral** administration. Elias teaches **topical** pharmaceutical compositions comprising 0.1 to 50% cyclosporin. Accordingly, none of the Kaswan, Elzinga et al. or Elias references provides any teachings within the scope of the presently pending method claims, all of which recite administration of cyclosporin -- DMSO compositions by intravascular injection, intracerebroventricular or intrathecal CSF injection or inhalation in which DMSO comprises at least 80% of the composition.

Turning to Broadwell et al., a full and accurate reading of this reference further reveals that it strongly teaches away from the presently pending claims directed to methods for administering cyclosporin -- DMSO. In particular, Broadwell et al. teaches that mice injected in the tail vein with a bolus of horseradish peroxidase dissolved in solutions comprising up to 15% DMSO showed no adverse side effects. But Broadwell also discloses that, although mice injected with solutions comprising 20-30% DMSO tolerated the injection, they later exhibited anterior pituitary

and cortical hemorrhages and poorly preserved cell and organelle membranes. (Broadwell, page 165, left column, lines 3-8). Applicants point out that this disclosure of serious, adverse effects associated with injections of solutions comprising 20% or more DMSO is both: i. completely ignored by the Examiner in the obviousness analysis, and ii. strongly teaches away from the presently claimed methods for administering by injection cyclosporin -- DMSO compositions that are at least 80% DMSO.

Applicants emphasize the fact that, although Broadwell et al. does state that "regardless of the volume, concentration, and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver and intestines of all DMSO injected mice appeared normal on gross examination at autopsy,"[1] **the lack of any adverse impact of DMSO injections on the particular, listed organs does not negate the fact that Broadwell et al. expressly teaches that injections of solutions comprising 20% or more DMSO have the seriously adverse effects of brain hemorrhages and organelle membrane degradation**. Accordingly, Broadwell et al. teaches a skilled artisan that injections of solutions comprising more than 15% DMSO should not be performed. Thus full and proper consideration of Broadwell, taken together with the other cited references, leads to a conclusion that the present invention represents an unobvious inventive step and therefore the instant rejection should be withdrawn.

Moreover, **Broadwell et al. does not teach or suggest any other injection site than the tail vein or peritoneum**, and therefore the combination of references cited by the Examiner in the obviousness analysis is completely silent in regard to the injection sites recited in independent claims 3 and 4. Applicants caution the Examiner that these claimed injection sites must be considered in the obviousness analysis. Applicants emphasize that the full consideration of these claimed injection sites leads to a determination that the Examiner has failed to establish *prima facie* obviousness against claims 3 and 4.

Finally, Applicants point out that none of the references cited by the Examiner in the obviousness analysis teach or suggest the administration of cyclosporin -- DMSO compositions by inhalation, as recited in instant claim 6. So even the combination of Kaswan, Elzinga et al., Broadwell et al. and Elias does not teach instant claim 6, and the Examiner has therefore failed

to make a showing of *prima facie* obviousness against claim 6.

In view of the foregoing discussion Applicants have established that the prior art cited in the obviousness analysis of the November 16, 2007 Office Action strongly teaches away from the presently pending claim 5, directed to methods of administering by vascular injection cyclosporin -- DMSO compositions that are at least 80% DMSO. Applicants have also established that the same prior art entirely fails to teach instant claims 3 and 4, directed to methods of administering by injection directly into the cerebrospinal fluid, brain and spinal cord cyclosporin—DMSO compositions that are at least 80% DMSO, and also instant claim 6, directed to methods of administering by inhalation cyclosporin -- DMSO compositions that are at least 80% DMSO. The presently pending claims are therefore nonobvious, and Applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection.

2. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request immediate allowance of the application, the claims of which define subject matter that meets all statutory patentability requirements.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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[1] Page 165, left column, lines 16-21.